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(54) Enantiomer separation

(57) The invention involves configurationally uniform, enantiomerically pure pyridylmethylsulfinyl-1H-benzimidazoles, a process for their manufacture and new intermediates which are necessary for the process.

Description

Area of application of the invention

The invention involves a process for separating chiral pyridylmethylsulfinyl-1H-benzimidazoles into their enantiomers. The enantiomers are used in the pharmaceutical industry for the manufacture of medications.

Prior art

A large number of patent applications and patents describe pyridylmethylsulfinyl-1H-benzimidazoles that possess gastric acid secretion-inhibiting properties. In connection with the invention in question, the following patent applications and patents are mentioned here as examples: EP-B-5 129, EP-A 1 34 400 (= USP 45 55 518), EP-A-1 27 763 (= USP 45 60 693), EP-B-1 66-287 (= USP 47 58 579), EP-A 1 74 726, EP-A-2 01 575 (= USP 46 86 230), WO89/05 299 and WO89/11 479. — It is further known that these pyridylmethylsulfinyl-1H-benzimidazoles have a chirality center and that they therefore should be separable into their enantiomers. Despite the large number of patent applications in the field of pyridylmethylsulfinyl-1H-benzimidazoles, until now no process has been described by means of which the pyridylmethylsulfinyl-1H-benzimidazoles could be separated into the optical antipodes. Also, the enantiomers of pyridylmethylsulfinyl-1H-benzimidazoles have so far not yet been isolated and characterized (due to the lack of a suitable separation process).

Description of the invention

A process has now been found by means of which the pyridylmethylsulfinyl-1H-benzimidazoles indicated hereafter in more detail can be separated into their optical antipodes.

The process is characterized in that one reacts compounds of formula I,

[see original for formula]

in which
R1 represents hydrogen, 1-4C alkyl or 1-4C alkoxy,
R2 represents hydrogen, trifluoromethyl, 1-4C alkyl, 1-4C alkoxy, completely or predominantly fluorine-substituted 1-4C alkoxy, chlorodifluoromethoxy, 2-chloro-1,1,2-trifluoromethoxy or, if desired, jointly with R3 completely or partially fluorine-substituted 1-2C alkenedioxy or chlorotrifluoroethylenedioxy,
R3 represents hydrogen, 1-4C alkyl, 1-4C alkoxy, completely or predominantly fluorine-substituted 1-4C alkoxy, chlorodifluoromethoxy, 2-chloro-1,1,2-trifluoroethoxy or, if desired, jointly with R2 completely or partially fluorine-substituted 1-2C alkenedioxy or chlorotrifluoroethylenedioxy,
R4 represents hydrogen or 1-4C alkyl,
R5 represents hydrogen, 1-4C alkyl or 1-4C alkoxy and
R6 represents 1-4C alkoxy, completely or predominantly fluorine-substituted 1-4C alkoxy or benzyloxy, or their salts with bases with configurationally uniform, chiral compounds of formula II,

Rchi—X (II)

in which Rchi is a configurationally uniform, chiral group and X is a waste group, separates the obtained isomer or diastereomer mixture III,

[see original for formula]

in which R1, R2, R3, R4, R5 and R6 have the above-indicated representations and Rchi is a configurationally uniform, chiral group, and liberates the configurationally uniform, optically pure compounds I from the optically pure diastereomers via solvolysis in strongly acidic medium.

1-4C alkyl stands for straight-chain or branched alkyl groups; examples include the butyl, i-butyl, sec-butyl, t-butyl, propyl, isopropyl, ethyl and in particular the methyl group.

1-4C alkoxy stands for straight-chain or branched alkoxy groups; examples include the butoxy, i-butoxy, sec-butoxy, t-butoxy, propoxy, isopropoxy, ethoxy and in particular the methoxy group.

Examples of completely or predominantly fluorine-substituted 1-4C alkoxy include the 1,2,2-trifluoroethoxy, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy and in particular the 1,1,2,2-tetrafluoroethoxy, the trifluoromethoxy, the 2,2,2-trifluoroethoxy and the difluoromethoxy group.

If R2 and R3 jointly represent completely or partially fluorine-substituted 1-2C alkenedioxy or chlorotrifluoroethylenedioxy, the substituents R2 or R3 are bonded in adjacent positions on the benzo portion of the benzimidazole ring.

Examples of completely or partially fluorine-substituted 1-2C alkenedioxy are the 1,1-difluoroethylenedioxy (—O—CF_2—CH_2—O—), the 1,1,2,2-tetrafluoroethylenedioxy (—O—CF_2—CF_2—O—) and in particular the difluoromethylenedioxy (—O—CF_2—O—) and the 1,1,2-trifluoroethylenedioxy group (—O—CF_2—CHF—O—).

Compounds of formula II include principally all chiral, configurationally uniform compounds that are capable of reacting with compound I or its anion with splitting-off of the waste group X and whose Rchi group can be split off again smoothly and without an undesired side reaction after the diastereomer separation.

Waste groups X include in particular all nucleophilically detachable atoms or groups, such as for example halogen atoms (J, Br or in particular Cl) or hydroxyl groups (—O—SO_2—CH_3—O—SO_2—CF_3 or —O—SO_2—C_6H_4—p—CH_2) activated via esterification (e.g., with sulfonic acids).

Rchi groups include all configurationally uniform groups that can be derived from naturally occurring or synthetically available chiral compounds and which can be split off from compounds III via solvolysis under acidic conditions. Rchi groups include in particular

– glycosyl groups derived from glycopyranoses, glycofuranoses or oligosaccharides and which, if desired, are partially or completely protected by protective groups commonly used in carbohydrate chemistry, or
– chiral terpene alcohol groups coupled via the oxygen atom, or other chiral alcohol groups coupled via the oxygen atom,

which have a carbonyl group or in particular a methylene group on the oxygen atom which functions as the point of coupling.

Preferred Rchi groups are groups of formula IV

R'—O—CH_2— (IV)

in which R' together with the oxygen atom to which it is bonded is a glycosyl group, a chiral terpene alcohol group, or other chiral alcohol group.

Examples of glycosyl groups R'—O— include those groups that are derived from naturally occurring mono or disaccharides, such as arabinose, fructose, galactose, glucose, lactose, mannose, ribose, xylose, maltose, sorbose or N-acetyl-D-glucosamine.

Examples of chiral terpene alcohol groups R'—O— are in particular such groups that are derived from a naturally occurring or synthetically readily available terpene alcohol. Examples of such terpene alcohols include: isopulegol, neomenthol, isomenthol, menthol, carveol, dihydrocarveol, terpinene-4-ol, mirtenol, citronellol, isoborneol, borneol, isopinocampheol and in particular fenchol.

Examples of other chiral alcohol groups R'—O— include those groups that are derived from the following alcohols: mandelate, cinchonidine, cinchonine, ephedrine, methyl serinate, sitosterol, 3-hydroxy-2-methyl-methyl propionate and ethyl lactate.

The fenchyloxymethyl group is an especially preferred Rchi group.

Compound I is reacted with compound II in a manner familiar to the specialist. To increase the nucleophilicity of compounds I it is expedient to deprotonate them, i.e., to start with the salts of compounds I with bases. Examples of basic salts include sodium, potassium, calcium, aluminum, magnesium, titanium, ammonium or guanidinium salts, which can be obtained, for example, by reacting compounds I with the corresponding hydroxides (e.g., sodium hydroxide or potassium hydroxide) in a conventional manner.

The reaction of compounds I with compounds II is carried out in inert, protic or aprotic solvents. Examples of such suitable solvents are methanol, isopropanol, dimethyl sulfoxide, acetone, acetonitrile, dioxan, dimethylformamide and preferably N-methylpyrrolidone.

The reaction is preferably carried out — depending on the reactivity of compound II — at temperatures between –30°C and +100°C, in particular at temperatures between 0°C and 50°C.

The diastereomer mixture obtained after the reaction of I with II is separated in a per se known manner, for example via chromatography on suitable columns or preferably via fractionated crystallization.

Because of the prototropy in the benzimidazole portion of compounds I (the 5 and 6 positions on the one hand and the 4 and 7 positions on the other are identical to each other), the reaction with compounds II with a corresponding substitution pattern in the benzimidazole produces isomer mixtures. It is expedient to separate the isomers from each other even before the diastereomers are separated, for example via column chromatography on a suitable supporting material (e.g., silica gel) and with suitable eluants (e.g., ethyl acetate).

The configurationally uniform compounds I are liberated from the optically pure diastereomers III via solvolysis under strongly acidic conditions. Examples of reagents suitable for the solvolysis include strong highly concentrated acids (e.g., 60-100% sulfuric acid, concentrated hydrochloric acid, anhydrous or hydrous tetrafluoroboric acid, methanesulfonic acid, trifluoromethanesulfonic acid, phosphoric acid or perchloric acid), preferably about 90% sulfuric acid. The liberation preferably takes place at temperatures between 0°C and 40°C. During the working-up that follows the liberation, one proceeds advantageously so that the pH is raised as quickly as possible, for example by placing the strongly acidic solution in buffer solution or preferably in caustic soda.

The compounds of formula II are known, or they are available in a manner familiar to the specialist from known compounds in an analogous manner. For example, compounds II, in which Rchi has the representation of formula IV and X is a chlorine atom, can be produced via chloromethylation of corresponding alcohols [e.g., analogous to R. C. Ronald et al., J. Org. Chem. 45 (1980) 2224].

The compounds of formula III are new and are likewise a subject of the invention.

The configurationally uniform, optically pure compounds of formula I are likewise new and are therefore also a subject of the invention.

Examples of optically pure compounds of formula I that can be manufactured via the process in accordance with the invention and of appropriate intermediates III in accordance with the invention, using the substituent representations in the above formulas I and III, include in particular the following compounds of Table I below.

Table I

[see original for table]

[see original for table]

Especially preferred compounds that can be manufactured via the process in accordance with the invention are the compounds

(+)-5-difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole,
(–)-5-difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole,
(+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole,
(–)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole,
(+)-2-[[(3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl-1H-benzimidazole, and
(–)-2-[[(3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl-1H-benzimidazole,

and their salts with bases.

The following examples serve to elucidate the invention in more detail. The abbreviation h stands for hour(s), m.p. for melting point.

Examples

1. (+)-5-difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-[(+)-fenchyloxymethyl]-benzimidazole

One adds dropwise 27.5 g (0.136 mol) (+)-fenchylchloromethyl ether to a solution of 50 g (0.123 mol) (±)-5-difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt in 125 ml N-methylpyrrolidone at a temperature of 25–35°C within one hour. After 6 h the mixture is diluted with 500 ml water, the pH is set at 9.0 and three extractions are conducted with 100 ml dichloromethane each. The combined organic phases are washed with water, dried and completely vacuum-evaporated. The oily residue is chromatographed on silica gel (mobile solvent: ethyl acetate). One isolates 25.2 g (74%) of a diastereomer mixture of (+) and (–) 5-difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-[(+)-fenchyloxymethyl]-benzimidazole as a pale yellow, gradually crystallizing oil (Rf value in ethyl acetate is about 0.85). Recrystallizing four times from ethyl acetate/diisopropyl ether yields the title compound (9.0 g 71.4%) in the form of colorless crystals of m.p. 138–139°C [$[\alpha]_D^{22}$ = +155.2° (c = 1, chloroform)].

2. (+)-5-difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

1.0 g (1.8 mmol) (+)-4-difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]-sulfinyl]-1-[(+)-fenchyloxymethyl]-benzimidazole is charged in portions to 7 ml 90% sulfuric acid under stirring at 5-10°C. After complete dissolution the reaction mixture is added dropwise to 8N caustic soda solution under cooling, the pH is set at 7.5 and the mixture is extracted several times with dichloroethane. The combined extracts are washed with water, dried over magnesium sulfate and completely vacuum-evaporated. The red, oily residue is chromatographed over silica gel (dichloromethane/methanol) and subsequently crystallized from diisopropyl ether. One obtains 0.3 g

(44%) of the title compound as a colorless crystallizate of m.p. 147–148°C (decomposition) [$[\alpha]_D^{22}$ = +146.0° (c = 0.5, acetonitrile/methanol 1:1)].

3.

(–)-5-difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-[(–)-fenchyloxymethyl]-benzimidazole

According to the method described in example 1, after reacting 28 g (0.069 mol) (±)-5-difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt with 16.5 g (0.084 mol) (–)-fenchylchloromethyl ether in 75 ml N-methylpyrrolidone, one obtains after chromatography on silica gel (dichloromethane/methanol) 11.0 [g] (58%) of a diastereomer mixture of (+) and (–) 5-difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)-methyl]sulfinyl]-1-[(–)-fenchyloxymethyl]-benzimidazole. Multiple recrystallization from ethyl acetate/diisopropyl ether yields the title compound in the form of colorless crystals (4.0 g, 72%) of m.p. 138–139°C [$[\alpha]_D^{22}$ = –152.8° (c = 1, chloroform)].

4. (–)-5-difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

According to the method described in example 2, one obtains from 1 g (1.8 mmol) (–)-5- difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-[(–)-fenchyloxymethyl]-benzimidazole in 7 ml 90% sulfuric acid 0.25 g (36%) of the title compound of m.p. 144–145°C (decomposition) [$[\alpha]_D^{22}$ = –144.4° (c = 0.5, acetonitrile/methanol 1:1)].

5.

(+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[(+)-fenchyloxymethyl]-benzimidazole

According to the method described in example 1, one obtains from (±)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt (60 mmol) in 80 ml N-methylpyrrolidone after chromatography on silica gel (ethyl acetate) and after multiple recrystallization from ethyl acetate/diisopropyl ether 3.1 g (40%) of the title compound in the form of colorless crystals of m.p. 161°C (decomposition) [$[\alpha]_D^{22}$ = +103.0° (c = 1, chloroform)].

6. (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

According to the method described in example 2, one obtains from 0.51 g (1 mmol) (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-[(+)-fenchyloxymethyl]-benzimidazole in ml 90% sulfuric acid 0.15 g (43%) of the title compound as amorphous solid [$[\alpha]_D^{22}$ = +165° (c = 0.5, chloroform)].

Commercial applicability

According to the process in accordance with the invention, pyridylmethylsulfinyl-1H-benzimidazoles can be separated into their optical antipodes for the first time. Especially surprising with this development is the fact that the optically pure compounds are liberated from the diastereomers by means of highly concentrated mineral acids, although it is known that the pyridylmethylsulfinyl-1H-benzimidazoles are very acid-sensitive compounds.

The compounds produced in accordance with the invention are used as active ingredients for the treatment of gastrointestinal diseases. Regarding the mode of administration and dosage of the active ingredients, one is referred to European patent 1 66 287.

Claims

1. Configurationally uniform, optically pure compounds of formula I

[see original for formula]

in which
R1 represents hydrogen, 1-4C alkyl or 1-4C alkoxy,
R2 represents hydrogen, trifluoromethyl, 1-4C alkyl, 1-4C alkoxy, completely or predominantly fluorine-substituted 1-4C alkoxy, chlorodifluoromethoxy, 2-chloro-1,1,2-trifluoromethoxy or, if desired, jointly with R3 completely or partially fluorine-substituted 1-2C alkenedioxy or chlorotrifluoroethylenedioxy,
R3 represents hydrogen, 1-4C alkyl, 1-4C alkoxy, completely or predominantly fluorine-substituted 1-4C alkoxy, chlorodifluoromethoxy, 2-chloro-1,1,2-trifluoroethoxy or, if desired, jointly with R2 completely or partially fluorine-substituted 1-2C alkenedioxy or chlorotrifluoroethylenedioxy,
R4 represents hydrogen or 1-4C alkyl,
R5 represents hydrogen, 1-4C alkyl or 1-4C alkoxy and
R6 represents 1-4C alkoxy, completely or predominantly fluorine-substituted 1-4C alkoxy or benzyloxy, and their salts with bases.

2. Compound according to Claim 1, selected from the group consisting of
(+)-5-difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole,
(–)-5-difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole,
(+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole,
(–)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole,
(+)-2-[[(3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl-1H-benzimidazole, and
(–)-2-[[(3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl-1H-benzimidazole,
and their salts with bases.

3. Process for producing configurationally uniform, optically pure compounds of formula I according to Claim 1 and their salts, characterized in that one reacts racemates of compounds of formula I, in which R1, R2, R3, R4, R5 and R6 have the representations indicated in Claim 1, or their salts with bases, with configurationally uniform, chiral compounds of formula II

Rchi—X (II)

in which Rchi is a configurationally uniform, chiral group and X is a waste group, separates the obtained isomer or diastereomer mixture III,

[see original for formula]

in which R1, R2, R3, R4, R5 and R6 have the representations indicated in Claim 1 and Rchi is a configurationally uniform, chiral group, and liberates the configurationally uniform, optically pure compounds I from the optically pure diastereomers via solvolysis in strongly acidic medium and, if desired, subsequently converts them to salts with bases.

4. Process according to Claim 3, characterized in that one produces a compound selected from the group consisting of
(+)-5-difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole,
(–)-5-difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole,
(+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole,
(–)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole,
(+)-2-[[(3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl-1H-benzimidazole, and
(–)-2-[[(3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl-1H-benzimidazole,
and its salts with bases.

5. Intermediates of formula III,

[see original for formula]

in which R1, R2, R3, R4, R5 and R6 have the representations indicated in Claim 1 and Rchi is a configurationally uniform, chiral group.

6. Intermediates according to Claim 5, in which Rchi is a fenchyloxymethyl group.